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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,140	10/31/2005	Eva Kontsekova	SONN:065US	5448

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,140	KONTSEKOVA, EVA	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-34* is/are pending in the application.

4a) Of the above claim(s) *24-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The prior Office Action mailed 8/17/2007 was based upon the examination of the Group I, claims 24, and 29-30, as they are drawn to a type IIA truncated tau molecule. However, as stated by Applicants in the reply filed 11/28/2007, Group II (claims 33-34) was elected by Applicants with traverse, *and not Group I*, in the reply filed June 11, 2007. The examiner recognizes this mistake, and the following action is directed to the examination of the elected invention set forth in instant claims 33-34. Claims 24-32 are withdrawn as being directed to a non-elected invention.

Election/Restrictions

2. Applicant's election with traverse of Group II in the reply filed on June 11, 2007 is acknowledged. The traversal (as set forth in the reply filed 11/28/2007) is on the ground(s) that the instantly claimed invention is directed to a N-terminal and C-terminal doubly truncated tau protein, and that this isolated molecule makes a contribution over the prior art, and therefore provides a special technical feature that defines a contribution over the prior art, and therefore the restriction between Groups I and II should be withdrawn. This is not found persuasive because the amino acid sequence set forth in Ghetti et al. does represent a doubly truncated type IIa tau protein comprising a mutation in the N-terminal portion of the molecule and in the C-terminal portion of the molecule, i.e. having only three tandem repeats located in the carboxy-terminal half of the molecule, wherein the disclosed molecule retains the ability to bind microtubule domains, see SEQ ID NO: 7 of Ghetti et al. Therefore, contrary to Applicant's assertions, the invention set forth in Group I, and the noted breadth of the

claims, i.e. claims 24, and 29 are not limited to any particular amino sequence, and the exact nature of the truncation is not specifically defined, does not make a contribution over the prior art as defined by Ghetti et al.

3. Moreover, the doubly truncated tau molecule as set forth in SEQ ID NO: 1 of the instant application, is disclosed in the prior art, see Figure 22 of WO 96/30766 (see pct search report). Therefore, again, the doubly truncated tau molecule recited in instant claim 24 does not make a contribution over the prior art.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 33-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a transgenic mouse comprising a genome having a double truncated tau sequence integrated therein, does not reasonably provide enablement for making a transgenic animal of *any* species of animal, wherein the genome of said animal comprises a double truncated tau sequence integrated into the endogenous tau equivalent gene of said any species of animal, and further wherein said animal exhibits Alzheimer's disease associated risk factors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

6. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

(A) The instant claim 33 generically recites: "[A] transgenic animal expressing a molecule of claim 24." Claim 24 recites: "[A]n isolated N- and C-terminally double truncated tau molecule further defined as a type IA tau molecule, type IB tau molecule, type IIA tau molecule, or type IIB tau molecule." (It is noted that type IIA truncated tau molecules was elected by Applicants). Claim 34 recites "[A] method of screening or testing a candidate compound for utility in the treatment of Alzheimer's disease comprising obtaining a transgenic animal according to claim 33 and using the animal to screen or test the candidate compound." The scope of the claimed transgenic animal reads on any animal, including human, non-human, mammal, non-mammal, invertebrate, vertebrate, or etc., wherein said animal expresses a double truncated

mutant protein of the tau protein, including all allelic and polymorphic forms of this protein, and isolated from any organism. Furthermore, the scope of claim 34 requires that the transgenic animal, of any species, and expressing an undefined sequence encoding exhibit an Alzheimer's disease phenotype, such that the transgenic animal can be used in a screen for potential treatments for Alzheimer's disease.

The specification as filed in Example 14, and Figures 25A-25B, generically mention a transgenic animal expressing a double truncated tau protein. At page 63, paragraph #3 it states that "*[T]he animals used in this experiment are of specific genetic background characterized by spontaneous hypertension and other Alzheimer's disease associated risk factors, such as dys-lipidaemia or diabetes.*" Due to the generic description of the transgenic animal in Example 14, Applicant's example appears to be prophetic in nature. It is understood that "[T]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation....Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art." see MPEP § 2164.02. Additionally, it is noted that the transgenic animal described in Example 14 is disclosed as exhibit risk factors for Alzheimer's disease, there is no evidence that the described animals actually exhibited the disease, such that the transgenic animal would be useful as a model for Alzheimer's disease.

At the effective filing date of the present application (07/12/2002), the transgenic art was and continues to be unpredictable with respect to the generation of any

transgenic animal and transgene behavior *in vivo*. Transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, specific promoter/gene combinations, random transgene insertion and genetic imprinting (e.g., transcriptional silencing of a gene based on transmission from parent to offspring of repressive nucleosomal structures) (Sanders Williams et al., J. Appl. Physiol. 2000, p. 1125, col. 1, paragraph 3 and p. 1124, col. 2, paragraph 2). For example, Moreadith et al., (1997, J Mol Med pp. 208-216) teaches that several putative ES cells lines have been isolated from hamster, pig, sheep, cattle, rabbit, rat, mink, monkey and humans, but the technology was limited to mice (page 214, col. 1, paragraph 3, lines 5-12). Post filing art by Keefer et al., (2004, Animal Reproduction Science, pp. 5-12) brings similar insight into the lack of predictability of generating any transgenic animal as the author recognizes the inefficiency of pronuclear microinjection in transgenic techniques and the unpredictability of transgene expression when applied to generating cows, goats and sheep (p.6, last paragraph bridging to p. 7, paragraph 1). Moreover, Sigmund (Arterioscler. Thromb. Vasc. Biol., 2000, pp. 1425-1429) corroborates the lack of predictability of phenotypes in transgenic models when he discloses that the phenotype caused by a specific genetic modification is strongly influenced by genes unlinked to the targeted locus. Sigmund (Arterioscler Thromb Vasc Biol, 2000, p. 1425, col. 1, paragraph 2) teaches that even strain differences between mice carrying the same construct can profoundly influence the phenotype. Thus, the art of record does not provide enablement for the claimed invention of making and using any transgenic animal other than a transgenic mouse whose genome comprises a

transgene comprising a DNA construct encoding an N- and C-terminally truncated human tau protein. Thus at the time of the instant invention, the skilled artisan would have needed to engage in an undue amount of experimentation to implement the claimed invention without a predictable degree of success.

The instant specification fails to teach which specific amino acids to be substituted, deleted or inserted within the minimally truncated tau core, at which positions and in which combinations such that the encoded polypeptide derivative for N- and C-terminally truncated tau gene is still functional to yield results contemplated by Applicant. The skilled artisan understands that one nucleotide change in a DNA molecule or one amino acid change in the polypeptide encoded by the DNA molecule could result in the loss of its biological activity as demonstrated in the generation of sickle-cell anemia wherein one specific amino acid mutation gave rise to the inherited disease (Biochemistry, John Wiley and Sons, 1990, p. 126-129). Similarly, in discussing peptide hormones, Rudinger has stated that "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study (Page 6, Conclusions *In* J.A. Parsons, ed. "Peptide hormones", University Park Press, 1976). Post filing art teaches that even single-nucleotide polymorphism without affecting the amino acid sequence can affect folding of the protein and thus alter its function (Kimchi-Sarfaty et al., 2007, Science, pp. 525-528; p. 527, col. 3, last paragraph). Though the recombinant technology for the generation of new mutant proteins is highly developed, the ability to determine *a priori* whether a

mutation and/or deletion and/or insertion will generate a functional protein is not predictable. Since the relationship between a sequence of a peptide and its tertiary structure is not well understood and is not predictable, it would require undue experimentation for one skilled in the art to determine alternative sequences of N- and C-terminally truncated tau protein molecules, such that transgenic animal expressing this truncated protein would produce an animal model suitable for isolating therapeutic candidates for the treatment of Alzheimer's disease.

In so far as the expression of a transgene, it was also well known in the art at the time of filing that expression of a gene of interest in a transgenic animal requires operable linkage of the gene to a promoter that controls gene expression (Kappel, Current Biology, 1992, entire document, specifically, p. 349, col. 2 paragraph 1). Additionally, it was well known in the art that not all promoters result in efficient expression or expression at levels in the appropriate tissues to result in a phenotype that is useful (Williams et al., (J. Appl. Physiol., 2000, p. 1124, col.2, lines 15-19). Logan et al., (1999, Clinical and Experimental Pharmacology and Physiology, p. 1021, col. 2, paragraph 2) further corroborates that the challenge in the development of transgenic animals in not in the process, but the design of the construct that will allow for the expression of the gene of interest in the desired cell type at an appropriate level. Therefore, it is clearly set forth in the art that for effective expression of a gene of interest in tissue specific manner, it is necessary to link the gene of interest to the appropriate tissue specific promoters. Thus, since Applicant's have not provided the appropriate guidance in this regard, the skilled artisan would have to resort to de novo

experimentation to practice the full scope of the claimed invention.

Due to the breadth of the claimed invention, the limited and prophetic guidance in the specification as filed, and the unpredictability associated with the production of a transgenic animal exhibiting a phenotype that correlates with risks factors associated with Alzheimer's disease, the skilled artisan would have to undertake undue experimentation to practice the full scope of the claimed invention.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 33-34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-21 of copending Application No. 10/521049. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant

application and those of the copending application are both drawn transgenic animals that express a double truncated tau molecule. The scope of the instant claims generally reads on any isolated double truncated tau molecule expressed in a transgenic animal, however, the scope of the claims of the copending application read on transgenic animals that comprise a cDNA molecule comprising SEQ ID NO: 9, which encodes a specific form of double truncated tau protein. Therefore the scope of the transgenic animal recited in the instant claims is anticipated by the claims of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Notice of references Cited

9. With the exception of WO 9630766A1, provided with the foreign search report, all other references cited above were previously forwarded to Applicants during the prosecution of copending application 10/521,049.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Ford/
Primary Examiner
Art Unit 1633

JLE